REACTIONS OF 1,4-DICHLOROBUT-2-YNE DERIVATIVES LEADING TO HETEROCYCLES

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Abstract - This short review summarizes the syntheses of various types of chrom-3-ene derivatives by hydration of acetylenic linkage and polyheterocycles such as benzofuro[3,2-c]benzopyrans, benzofuro[3,2-b]benzofurans, benzofuro[2,3-b]-benzofurans and a number of other heterocyclic systems by [3,3] sigmatropic rearrangements from 1,4-dichlorobut-2-yne derivatives.

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1. INTRODUCTION

Quite a good amount of work has been carried out on the reactions of 1,4-dichlorobut-2-yn (1) derivatives since its preparation\(^1\) from but-2-yn-1,4-diol by Johnson. For synthesis of heterocyclic compounds mainly two different reactions were utilized viz. (i) Claisen rearrangement of various 1,4-diaryloxybut-2-ynes and 4-aryloxybut-2-yn-1-ylxyheterocycles, (ii) hydration of various 1,4-disubstituted derivatives of 1,4-dichlorobut-2-yn. In 1963 Thyagarajan et al. initiated the work on 1,4-diaryloxybut-2-yn and subsequently developed it into a reaction of synthetic utility for the synthesis of heterocycles viz. chrom-3-ene derivatives, benzofuro[3,2-c][1]benzopyrans (11a-methylpterocarps), benzofuro[3,2-b]benzofurans and benzofuro[2,3-b]benzofurans. The reactions are fascinating because the but-2-ynyl derivatives in most of their reactions viz. hydration followed by cyclization, or Claisen rearrangement followed by cyclization give isomeric products. Consequently various heterocycles can be synthesized in an unconventional manner by simple molecular reorganizations. This short review is limited to present only the aforesaid two reactions of 1,4-dichlorobut-2-yn derivatives yielding heterocycles. This part does not include the amine oxide and sulfoxide rearrangements of \(N\)-alkylanilino and arylthio derivatives which will form part two of the review and will be communicated later.

2. Preparation of 1,4-dichlorobut-2-yn derivatives.

1,4-Bis-derivatives of 1,4-dichlorobut-2-yn are generally prepared from 1,4-dichlorobut-2-yn (1) by the nucleophilic displacement of chlorides by aryloxy anion. 1,4-Diaryloxybut-2-ynes (2) are prepared according to the procedure\(^1\) of Johnson et al.

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{R}^3 & \quad \text{R}^4
\end{align*}
\]

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{EtOH, } & \quad \Delta
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{R}^1 \\
\text{O} & \quad \text{R}^2 \\
\text{R}^3 & \quad \text{R}^4
\end{align*}
\]

1-Aryloxy-4-arylthiobut-2-ynes (4) were prepared by the addition a solution of 1-aryloxy-4-chlorobut-2-yn (3) in ethanol to a solution of arylmercaptan and potassium hydroxide in ethanol under nitrogen at room temperature.\(^2,3\)

Corresponding sulfoxides and sulfones were prepared by selective oxidation with one or two equivalents of \(m\)-chloroperoxybenzoic acid in dichloromethane.
Other unsymmetrical 1,4-disubstituted but-2-ynes are usually prepared from 1-aryloxy-4-chlorobut-2-ynes\textsuperscript{4,5} (3) by replacing the chloride with an oxy anion on a heterocyclic moiety. This may be achieved by classical alkylation procedure\textsuperscript{5} \textit{i.e.} by refluxing 1-aryloxy-4-chlorobut-2-yne (3) and the appropriate heterocyclic compound with a hydroxy group at a suitable position in acetone in the presence of anhydrous potassium carbonate or by phase transfer catalyzed alkylation condition\textsuperscript{7} \textit{i.e.} by stirring a solution of 1-aryloxy-4-chlorobut-2-yne (3) and the appropriate heterocyclic compound with a hydroxy group at a suitable position in dichloromethane and sodium hydroxide solution at room temperature in the presence of a phase transfer catalyst (PTC) such as benzyltriethylammonium chloride or tetrabutylammonium bromide.\textsuperscript{8} Classical alkylation proved to be better for obtaining $O$-alkylated products in case of ambident nucleophiles. In some cases PTC condition resulted $C$-alkylation, $C,C$-dialkylation in preference to $O$-alkylation.\textsuperscript{8,9}

3. \textbf{Synthesis of heterocycles by hydration of acetylenic linkage of 1,4-bis-derivatives of 1,4-dichlorobut-2-yne.}

Hydration of alkynes has long evoked interest as a synthetic reaction of value\textsuperscript{10-12} catalyzed by mineral or Lewis acids and mercuric ion, the products of such hydration have variously afforded ketones,\textsuperscript{13} enol acetates,\textsuperscript{14} ketols\textsuperscript{15} and heterocyclic ring products.\textsuperscript{16} This reaction has been successfully employed for the synthesis of 4-substituted chrom-3-ene from 1,4-dichlorobut-2-yne derivatives viz. 1,4-bis(aryloxy)but-2-ynes (2a-m), 1-aryloxy-4-arylthiobut-2-ynes (4a-o) and 1-aryloxy-4-arylsulfonylbut-2-ynes (5a-o).

3.1 \textbf{Hydration of 1,4-diaryloxybut-2-ynes (2).}

Hydration of 1,4-diaryloxybut-2-ynes\textsuperscript{17} (2a-m) with red mercuric oxide in refluxing acetic acid in the presence of concentrated sulfuric acid afforded 4-aryloxymethylchrom-3-ene (6a-m) (Scheme 1). Hydration of 2 with mercuric oxide and sulfuric acid was remarkable because simple phenyl propargyl ether (8) affords only phenoxyacetone (9) under identical condition. Other route\textsuperscript{18} for the syntheses of 4-aryloxymethylchrom-3-ene is a much longer one starting from 4-chlorobut-2-yn-1-ol\textsuperscript{19} (Scheme 2). This approach of synthesis of aryloxymethylchrom-3-ene derived additional interest in view of a report on the biological activity of 1-aryloxymethyl-3,4-dihydroisoquinolines (15). The latter compounds have been
shown to possess strong inhibitory effect on the component enzyme, viral neuraminidase, present in common respiratory pathogenic viruses. So the potential of analogous systems were investigated.
Contrary to earlier experience at hydration of the acetylenes utilizing mercuric sulfate as the preferred catalyst, it was found that a combination of red mercuric oxide and a few drops of sulfuric acid in acetic acid medium afforded more clean and better products.\textsuperscript{17} The 4-aryloxymethylchrom-3-enes (6a-m) were unstable to prolonged heating in acid.\textsuperscript{17} There is an optimal reaction time for the hydration to proceed without much destruction of the product formed. Of the several 1,4-diaryloxybut-2-ynes (2a-m) studied, there were three which not only gave the chromens (6a-m) but also the thermally equilibrated exomethylene isomers (7j-l) (Scheme 1).\textsuperscript{17}

### 3.2 Hydration of 1-aryloxy-4-arylsulfonylbut-2-ynes (5).

The aforesaid one step synthesis of chrom-3-enes (6a-m) was extended to the hydration of 1-aryloxy-4-arylsulfonylbut-2-ynes (5a-o).\textsuperscript{21} The availability of two different modes of cyclization to these unsymmetrical substrates (5a-o) generated additional interest.

\begin{equation}
\text{Scheme 3}
\end{equation}

Treatment of the substrates (5a-o) with red mercuric oxide and sulfuric acid in refluxing acetic acid gave only one type of products (16a-o) of cyclization out of the two different possibilities.\textsuperscript{21} When compared with the corresponding 1,4-diaryloxybut-2-ynes (2a-m), the sulfones (5a-o) gave higher yields of chrom-3-enes\textsuperscript{22} (16a-o) because of varying stabilities of the respective chrom-3-enes in the acidic reaction
medium. Perhaps, the sulfone function has directive influences on the mode of cyclization to give only one type of products (Scheme 3).

3.3 Hydration of 1-arylxy-4-arylthiobut-2-ynes (4).

The facility of cyclization of 2a-m and 5a-o to chromenes in the aforesaid reactions, prompted further investigation on the analogous synthesis of thiocromenes from 1-arylxy-4-arylthiobut-2-ynes (4a-e) and 1,4-bis(arylthio)but-2-ynes (17). The hydration of 1-arylxy-4-arylthiobut-2-ynes (4a-e) was investigated using hot glacial acetic acid as solvent alongwith red mercuric oxide and a trace of concentrated sulfuric acid as catalysts. Of the five substrates (4a-e) examined each gave a single product. One of these was readily identified as the chromene (18a) by its facile oxidation to 16a reported earlier. Each of the other four products (19b-e) on oxidation with m-chloroperoxybenzoic acid afforded corresponding sulfones (20b-e). Interestingly, chromatography of these sulfones over basic alumina (or treatment of a d<sup>3</sup>-chloroform solution with dilute alkali in an NMR tube) resulted in a quantitative conversion into the chrom-3-enes (16b-e). The sulfones (20b-e) were, however, quite stable to chromatography over neutral alumina. Isomerization of a vinylic sulfone into the corresponding allylic

![Scheme 4](image)
sulfone during chromatography has been reported\(^2\text{5,26}\) previously. Additional corroboration of vinyl sulfone structure in the sulfone (20b-e) was readily obtained by an aluminum amalgam reduction of the vinyl sulfone to the 4-methylenechroman (21b-e) (Scheme 4).\(^2\text{3}\)

An interesting observation in the formation of the chrom-3-ene is the fact that, both with sulfides (4a-e) and the sulfones (5a-o), the initial product of the cyclization is the chrom-3-ene.\(^2\text{3}\) Acid catalyzed equilibration of the sulfide, however, results in conversion to the exomethylene product.\(^2\text{3}\) The geometrical disposition of the sulfone with respect to the benzene ring of the chrom-3-ene was found to be trans by the reduction of sulfone (20d) with aluminum amalgam in deuterium oxide at low temperature. This led to the cleavage of the sulfone function and incorporated a deuterium atom in its place. The \(^1\text{H}-\text{NMR}\) spectrum of this product (22), readily revealed the site of the deuterium atom as shown in Scheme 5.\(^2\text{3}\)

![Scheme 5](image)

The specific location of deuterium was found to be temperature dependent. Reduction of the sulfone (20d) at temperature above 0 °C resulted in scrambling of the deuterium on the terminal methylene leading to mixtures of 22 and its geometrical isomer. The hydration of 1-aryloxy-4-arylthiobut-2-ynes (4a-e) demonstrated a well-defined preference for formation of a 6-membered oxygen heterocycle and none of possible thiochrom-3-ene derivative.\(^2\text{3}\)

### 3.4 Hydration of 1,4-bis(arylthio)but-2-ynes (17).

The mercuric ion-catalyzed hydration of 1,4-bis(arylthio)but-2-ynes (17a-f) under the same reaction conditions as stated earlier, revealed a different picture, no cyclic product was obtained even in the absence of any competing aryloxy function. This reaction afforded a variety of products in acetic acid among which are : 1,4-bis(arylthiomethyl)vinylacetate (28), 1,4-bis(arylthio)-2-butanone (25), 1-arylthio-3-buten-2-one (26) and 1-arylthio-4-acetoxy-2-butanone (27).\(^2\text{3}\) Ketone (25) eliminates aryl thiol\(^2\text{7-30}\) in an acidic medium yielding 26 which undergoes Michael addition of solvent to give 27. Hydration of 17a-f in methanol cleanly gave 1-arylthio-4-methoxy-2-butanones (29) (Scheme 6).\(^2\text{3}\)

Thus a study of the hydration of 1,4-bis(arylthio)but-2-ynes (4a-e) has failed to reveal formation of any thiochrom-3-enes. The failure indicates relatively less activation of the site of ring closure by the sulfide sulfur than oxygen in the aryl propargyl ethers. To examine this point, the hydration of 1,4-bis(arylsulfonyl)but-2-ynes\(^3\text{1}\) (31a-g) was investigated. The hydration of the alkyne (31a-g) is found to be
straightforward and simple. The products from hydration of 31a-g are ketones (32a-g) obtained in high yields and purity. This result provides emphatic evidence for the need for an activating function in the alkyne to observe any ring closure. Ketones (32a-g) are extremely stable to the acidic hydration conditions, although under mildly alkaline conditions, they are susceptible to elimination-addition sequence (Scheme 7).27

### Scheme 6

### Scheme 7

3.5 Hydration of 1-arylsulfonylbut-2-ynes.

Similar results implicating the need for an activating function in the alkyne to undergo any ring closure,
were observed in a study of hydration directed to the regiospecific hydration in arylsulfonylbut-2-ynes (37a-c) (Scheme 8). Mercuric ion catalyzed hydration of 1-arylsulfonylbut-2-yne (37a), 1-arylsulfonyl-4-chlorobut-2-yne (37b) and 1-arylsulfonyl-4-arylthiobut-2-yne (37c) leads to a single ketonic products (38a-c) (Scheme 8). Evidence has been provided to show that the reaction is truly regiospecific, with consistent placement of the carbonyl ω- to the sulfonyl group.

\[
\begin{align*}
\text{PhSO}_2 & \quad \text{HgO, } \text{H}_2\text{SO}_4, \text{AcOH, } \Delta \\
\text{R} & \quad \text{PhSO}_2 \\
37\text{a, } R = \text{Me} & \quad 38\text{a, } R = \text{Me} \quad 73.7 \\
\text{b, } R = \text{CH}_2\text{Cl} & \quad \text{b, } R = \text{CH}_2\text{Cl} \quad 63.1 \\
\text{c, } R = \text{CH}_2\text{SAr} & \quad \text{c, } R = \text{CH}_2\text{SAr} \quad 29.0
\end{align*}
\]

Scheme 8

An interesting hydration of 1,6-diaryloxy-2,4-hexadiyne (39) to give 4,4'-bichrom-3-ene (40) was reported\(^2\) by Balasubramanian et al. (Scheme 9).

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

Scheme 9

Despite variations of results, the butynyl bis(sulfides) (17a-f) offer some clue to the overall mechanism of the ring closure under hydration conditions. Although ketonic products are obtained from bis(sulfides) (17a-f), no ring closure derivatives are detected.\(^2\) This is in contrast to the fact that ring closed products are obtained from 1-aryloxy-4-arylthiobut-2-ynes (4a-e) and their sulfones (5a-o), but no ketonic products are detected among the hydration products.\(^2\)\(^1\)\(^2\) Thus formation of the ketones and the chrom-3-ynes may be by entirely separate pathways. This has been verified by Bates ans Jones\(^3\) by preparing a number of 1,4-diaryloxy-2-butanone and subjecting them to hydration conditions and found that none produce 4-aryloxymethylchrom-3-ene (6). Bates et al. proposed an additional mechanism involving concerted sigmatropic rearrangement triggered by the charge induced π-complex formation.\(^4\)

Another possibility involving a σ-complex, cyclization of this ion (41), and protonolysis of the C-Hg bond\(^5\) produced a "two-step" sigmatropic mechanism which may be viewed as a metal ion catalyzed
Friedel-Crafts alkenylation of an aromatic ring by an alkyne. However, 'pathway b' was discarded on the basis of experimental evidences.

4 [3,3] Sigmatropic rearrangements of 1,4-dichlorobut-2-yne derivatives.

1,4-Diaryloxybut-2-ynes (2) can undergo two consecutive Claisen rearrangements. Usually these give products of two sequential rearrangements whereas 1-aryloxy-4-vinylxybut-2-ynes afford products of the first Claisen rearrangement at a relatively much lower temperature (100-130 °C). However, the products of the second Claisen rearrangements can be obtained at a much higher temperature (above 200 °C).

4.1 Regioselective synthesis of 2H-pyrano- and furoheterocycles.

So far we have seen that the formation of 2H-pyrane ring fused to aryl ring can be achieved by mercury(II) catalyzed hydration of 1,4-diaryloxybut-2-ynes (2). If the arylxybut-2-ynylxy function is attached to a vinyl group, the activation energy requirement is much less compared to that of aryl propargyl ether and the first [3,3] sigmatropic rearrangement occurs at a much lower temperature \( ca. 132 \) °C. This has been utilized for the synthesis of 2H-pyrane ring or furan ring fused to a number of heterocycles viz. coumarin, quinolone, uracil etc.

4.1.1 Regioselective synthesis of 2H-pyranoheterocycles.

The synthesis of 2H-pyranoheterocycles from the 1,4-dichlorobut-2-yne derivatives by the application of [3,3] sigmatropic rearrangement at a relatively low temperature is simple and has been proved to be a general method. The following 2H-pyranoheterocycles have been synthesized by this protocol.


The ethers, 1-aryloxy-4-(4'-coumarinyloxy)but-2-ynes (45a-h) were heated in refluxing chlorobenzene to
give pyrano[3,2-c][1]benzopyran-5(2H)-ones (46a-h) in almost quantitative yields. All the fourteen butyne derivatives studied expectedly underwent [3,3] sigmatropic rearrangement at the 4-(4'-coumarinyl-ox)propynyl part to give pyranocoumarin derivatives (46a-h) and no furocoumarin was formed at all\textsuperscript{39} (Scheme 11).

Scheme 11

Flindersine, 2,2-dimethylpyrano[3,2-c]quinolin-5(2H)-one (50) and various substituted flindersine derivatives are widely distributed in nature.\textsuperscript{40-45} A good deal of work has been reported on the synthesis of flindersine\textsuperscript{46-49} and its analogs with various substitution in the aromatic ring.\textsuperscript{50-52} A simple methodology for the regioselective synthesis of flindersine analogues, pyrano[3,2-c]quinolin-5(2H)-ones (52a-c) with variation in the dihydropyan ring has recently been reported\textsuperscript{53} (Scheme 11) \textit{via} the thermolysis of 4-(1-aryloxybut-2-ynyl)quinolin-2(1H)-ones (51a-c). This method is perhaps the simplest route for the synthesis of these heterocycles. It is remarkable to note that even when 4-hydroxy-1-methylquinolin-2(1H)-ones (53) are refluxed with 1-aryloxy-4-chlorobut-2-ynes in acetone /1-butanol, cyclic products\textsuperscript{53} such as 54 and 55 are obtained. The geometrical disposition of the vinylic hydrogens H\textsubscript{a} and H\textsubscript{b} of
products (54) and (55) respectively has been established from their $^1$H-NMR chemical shifts. The butyne derivative containing aryloxy moiety carrying a methyl group$^{54}$ at the para-position (45m) afforded the normal pyranocoumarin (46m) along with its isomer (56m). The one with the methyl group at the ortho-position (45n) also gave the normal pyranocoumarin (46n) along with its isomer (57n) (Scheme 12). However, other substrates containing aryloxy moiety carrying methyl substituents (45i-l) afforded the normal pyranocoumarin (46i-l) (Scheme 11). The formation of 57n from 45n may be explained by an initial [3,3] sigmatropic rearrangement to give 47 followed by isomerization of the allene moiety to butadiene (58) by a 1,3-H$^+$ shift$^{55,56}$ and acid catalyzed cyclization (enol may also act as an acid) of 59 to 57n (Scheme 12). The products (46) and (52) are also formed from intermediate (47) via enolization followed by [1,5] H shift and electrocyclic ring closure (ECR) (Scheme 11). Compound (57n) is formed in preference to product (46n), product ratio is not altered even if the reaction is carried out in purified chlorobenzene or in the presence of hydroquinone or p-toluenesulfonic acid. The formation of 56m from 45m may be rationalized via the formation of butadiene (58) followed by enolization and 6-endo cyclization to give 56m.

\[
\begin{align*}
\text{45m,n} & \xrightarrow{[3,3]} \text{47} & \text{58} & \xrightarrow{\text{H}^+} \text{61} \\
\text{57n, Ar} = \text{o-tolyl} & \xrightarrow{\text{6-endo cyclization}} \text{56m, Ar} = \text{p-tolyl}
\end{align*}
\]

Scheme 12

Regioselective Synthesis of Thiopyrano[2,3-b][1]benzo thiopyran-5(2H)-ones (65).

Efforts towards the synthesis of pyrano[3,2-c][1]benzothiopyran-5(2H)-thione (62) starting from 4-hydroxydithiocoumarin$^{57}$ (63) were unsuccessful. Any attempts to secure O-alkylated products from 4-hydroxydithiocoumarin (63) and allyl halides or but-2-ynyl halides by classical alkylation or phase-transfer
catalyzed alkylation failed. Only product obtained was 2-allylthio[1]benzothiopyran-4-ones or 2-(4'-aryloxybut-2-ynythio[1]benzothiopyran-4-ones (64) in almost quantitative yields. Mainly S-alkylation was observed, C-alkylation to a limited extent and virtually no O-alkylation although compound (63) is capable of forming an ambident anion with several canonical forms A, B, and C, or delocalized D.

For achieving O-alkylation the Mitsunobu reaction was attempted. Here too the nucleophilicity of sulfur became the deciding factor and only the S-alkylation was observed. The S-alkylated products, 2-but-2-ynythio[1]benzothiopyran-4-ones (64a-i) on refluxing in chlorobenzene furnished 4-substituted methylthiopyrano[2,3-b][1]benzothiopyran-5(2H)-ones (65a-i) in excellent yields (Scheme 13).

The synthesis of thiopyrano[2,3-b]benzothiopyran-5(2H)-ones (65) is very much related to the synthesis of thieno[2,3-b]benzothiopyran-4-one reported earlier by a longer route. Thieno[2,3-b]benzothiopyran-4-one skeleton has been used as an intermediate for the synthesis of a series of drugs which are useful for the treatment of Psychotic disturbances.

**Regioselective Synthesis of Pyrano[3,2-d]pyrimidine-2,4-dione.**

8-Aryloxymethyl-1,3-dimethyl-6H-pyrano[3,2-d]pyrimidine-2,4-diones (67a-f) were synthesized in 88-92 % yields by the thermal [3,3] sigmatropic rearrangement of 5-(4-aryloxybut-2-ynyloxy)-1,3-dimethylpyrimidine-2,4-diones (66a-f) in refluxing chlorobenzene (purified) for 2-4 h (Scheme 14). This method is better than that of Otter et al. who reported the varying proportions of furo[3,2-d]pyrimidine-2,4-dione and 6H-pyrano[3,2-d]pyrimidine-2,4-dione (67, R = H) from the thermal reaction of 5-(2-propynloxy)uracil (66, R = H).
Regioselective Synthesis of Pyrano[2,3-c][1]benzopyran-5(3H)-ones (69) and 3H-Pyrano[2,3-c]quinolin-5(6H)-ones (74).

These heterocycles are also synthesized by the thermal sigmatropic rearrangement of propargyl and but-2-ynyl ethers of 3-hydroxycoumarin and 3-hydroxyquinolone. A regioselective synthesis of pyrano[2,3-c][1]benzopyran-5(3H)-one derivatives (69a-i) from 3-(4-aryloxybut-2-ynoxy)1 benzopyran-2-ones (68a-i) has been achieved via the pericyclic pathway. If ionic or radical pathway is allowed to follow then the corresponding 2-methylfuro[2,3-c][1]benzopyran-4-one derivatives are obtained. Substrates (68a-i) in refluxing chlorobenzene undergo an initial [3,3] sigmatropic rearrangement followed by enolization to give the allenyl enols (71). In the absence of any other agents (acid, base or radical initiator) normally the pericyclic pathway (i.e. [1,5] H shift followed by electrocyclic ring closure) is followed to give 1-aryloxymethylpyrano[2,3-c][1]benzopyran-5(3H)-ones (69a-i) in almost quantitative yields (Scheme 15). When this reaction was conducted in commercial chlorobenzene without further purification, a mixture of furo- and pyranocoumarins are obtained. The products are characterized by the application of spectroscopic methods e.g. high resolution 1H-NMR and 13C-NMR spectra.

The same methodology has been successfully utilized for the synthesis of a number of 3H-pyrano[2,3-c]quinolin-5(6H)-ones (74a-e) in almost quantitative yields. While 3-propynoxyquinolin-2(1H)-ones gave exclusively the pyranquinolones, the 3-(4-aryloxybut-2-ynoxy)-1-methylquinolin-2(1H)-ones (73a-e) in refluxing chlorobenzene generated pyranquinolones (74a-e) or furoquinolones or a mixture of both. Addition of azoisobutyronitrile as a radical initiator or hydroquinone as a radical scavenger showed no effect on the formation of products.

4.1.2 Synthesis of 2H-Furoheterocycles

Instances of synthesis of furoheterocycles from 1,4-bis-derivatives of 1,4-dichlorobut-2-yn are less abundant in literature compared to that of pyrano heterocycles. Synthesis of 2-methyl-3-aryloxymethyl-
The facile formation of furo[3,2-c]quinolin-4(5H)-ones (78a-e) may be explained by the replacement of chlorine of 1-aryloxy-4-chlorobut-2-yne (3) by quinolin-2(1H)-one-3-oxy anion to give ethers (79) (not shown).
isolated) which under the reaction conditions suffered a [3,3] sigmatropic rearrangement to give allenyl enols (80). These intermediates under base catalysis afforded the furo[3,2-c]quinolin-4(SH)-ones (78a-e) (Scheme 16).

**Furo[2,3-c][1]benzopyran-4-one and furo[2,3-c]quinolin-4(5H)-ones.**

Simple 2-methylfuro[2,3-c][1]benzopyran-4-ones have been synthesized from 3-propynyloxy[1]benzopyran-2-one or 3-(2-chloroprop-2-enyloxy)[1]benzopyran-2-one or by dehydrogenation of 1,2-dihydrofuro[2,3-c][1]benzopyran-2-one. Recently it has been demonstrated that the intermediate allenyl enols (80) from the thermal [3,3] sigmatropic rearrangement of 3-(4-aryloxybut-2-ynyloxy)[1]benzopyran-2-ones (68a-i) may be cyclized regioselectively following a pericyclic pathway to give pyranocoumarins (69a-i), a radical pathway as well as an ionic pathway to give 1-aryloxymethyl-2-methylfuro[2,3-c][1]benzopyran-4-ones (81) (Scheme 17). This is the first instance where it has been shown that the intermediate allenlenols from Claisen rearrangement can be cyclized regioselectively following a radical pathway.

The synthesis of simple furo[2,3-c]quinolin-4(5H)-ones have been recently reported. The thermal [3,3] sigmatropic rearrangement of 3-(4-aryloxybut-2-ynyloxy)quinolin-2(1H)-ones (73a-e) in the presence of a base or p-toluenesulfonic acid afforded 1-aryloxymethyl-2-methylfuro[2,3-c]quinolin-4(5H)-ones (85a-e) (Scheme 17). Interestingly 1-aryloxymethyl-3H-pyano[2,3-c]quinolin-5(6H)-ones (74a-e) on heating in refluxing N,N-diethylaniline also provided 1-aryloxymethyl-2-methylfuro[2,3-c]quinolin-4(5H)-ones (85a-e).
Synthesis of furo[3,2-d]pyrimidine-2,4-diones.

Synthesis of 1,3-dimethyl-6-methylfuro[3,2-d]pyrimidine-2,4-diones has been reported.\textsuperscript{66,87} Substrates 5-(4-aryloxybut-2-ynyloxy)-1,3-dimethylpyrimidine-2,4-diones (66a-b, d, f, g) on heating in basic solvent e.g. \textit{N},\textit{N}-diethyladine at 130 °C furnished 7-aryloxymethyl-1,3-dimethyl-6-methylfuro[3,2-d]pyrimidine-2,4-diones (89a-b, d, f, g) in 72-80 % yields\textsuperscript{88,89} (Scheme 18). The formation of products 89a-b, d, f, g from 66 has been rationalized by a mechanism similar to that given for the formation of products 81 and

\begin{align*}
\textbf{Scheme 17}
\end{align*}
4.2 Double Claisen rearrangement of 1,4-diaryloxybut-2-ynes.

Syntheses of benzofuro[3,2-c][1]benzopyran, benzofuro[3,2-b]benzofuran and benzofuro[2,3-b]benzofuran have been achieved by thermal double (two consecutive) Claisen rearrangement of 1,4-diaryloxybut-2-ynes (2). We like to call this “Thyagarajan reaction” after the name of B. S. Thyagarajan for his outstanding contribution to the chemistry of derivatives of 1,4-dichlorobut-2-yne.

4.2.1 Synthesis of benzofuro[3,2-c][1]-6a,11a-dihydro-11a-methylbenzopyrans from 1,4-diaryloxybut-2-ynes.

Successful Claisen rearrangement of 1,4-bis(4-chlorophenoxy)but-2-yne (2a) in refluxing N,N-diethyl-aniline for 10-12 h was first reported by Thyagarajan and co-workers. The product of the rearrangement is the benzofuro[3,2-c][1]-6a,11a-dihydro-11a-methylbenzopyran (90a). Later the same group reported the rearrangement of a number of 1,4-diaryloxybut-2-ynes (2b-d, f-j, l-u) for the synthesis of the tetracyclic compounds resembling pterocarpans, more specifically 11a-methylpterocarpans (90b-d,f-j,l-u) (Scheme 19).

![Scheme 19](image)

Although the reaction is general for the synthesis of benzofuro[3,2-c]benzopyrans (90), 1,4-bis(4-nitrophenoxy)but-2-yne and 1,4-bis(4-formy1phenoxy)but-2-yne fail to give any tractable product, except tarry material perhaps due to the presence of aryloxy group with electron withdrawing substituents demanding higher activation energy.

The stereochemistry of the ring junction in the tetracyclic system can be surmised from molecular models.
which show a strain-free cis arrangement. The stereochemistry of the ring fusion of two oxygen heterocyclic ring in petrocarpan series was concluded to be cis from Dreiding models.\textsuperscript{91,92}

The $^1$H-NMR spectrum of benzofuro[3,2-c]benzopyran (90a-d, f-j, l-u) is interesting especially a multiplet between 3.35 and 4.50 ppm for the benzylic and O-methylene protons which shows a typical ABC pattern with a total of 11 lines. The nonequivalence of the OCH$_2$ protons shows for a coupling between themselves with $J = 11$ Hz while the benzylic proton shows a small coupling constant of 5 Hz with one of them and 8.5 Hz with the other. This feature was further confirmed when the benzylic proton was replaced with a bromine atom. In these the OCH$_2$ showed an AB quartet in the region 4.3-5.2 ppm with $J = 12$ Hz. The replacement of the benzylic proton by bromine (Scheme 20) aids in the determination of the geminal and vicinal coupling constants in the parent molecule. Such a bromination has not been reported in the pterocarpan derivatives.\textsuperscript{38} Extensive proton magnetic resonance study of several other pterocapan derivatives by Pachler and Underwood\textsuperscript{93,94} also showed that the stereochemistry of the ring junction is cis.

![Scheme 20](image)

These 11a-methylpterocarpans can undergo unusual ring contraction to benzofurobenzofuran (coumaranocoumaran) or a novel ring expansion to benzofurobenzoxepinone.\textsuperscript{95}

**Mechanism**

Initially Thyagarajan et al. proposed the following mechanism due to the presence of the coumaran moiety in the final products (90a). Two sequential Claisen rearrangements were considered leading to the formation of benzofuro[3,2-c][1]-6a,11a-dihydro-11a-methylbenzopyrans or shortly 11a-methylpterocarpans 90 (Scheme 21).
The well-established equilibrium between the anion of ortho-allenylphenol\(^{66}\) and 2-methylbenzofuran was suggestive of such a mechanism. Again, instances are known where an allylic unsaturation forming part of a ring system participates in a Claisen rearrangement.\(^{97,98}\) This suggestion was tested by synthesizing the intermediate (93) from 3-chloromethyl-2-methylbenzofuran\(^{99}\) and also by another route from 1,4-diaryloxybut-2-ynes\(^{90}\) and subjecting this to the condition of the rearrangement. However, the so-called intermediate 2-methyl-3-phenoxymethylbenzofuran (93) was recovered unchanged. 4-Phenoxymethylchrom-3-ene (6b) has been described earlier from the hydration of 1,4-bis(phenoxy)but-2-yne (2b).\(^{17}\) This has also been synthesized from 4-chloromethylchrom-3-ene (14) (described earlier by propargylic Claisen rearrangement\(^{100}\)) by the nucleophilic displacement of halogen by phenoxide anion (Scheme 2). This compound 6b on refluxing in N,N-diethyladiline afforded the same product 11a-pterocarpan as obtained from the direct rearrangement of 1,4-bis(phenoxy)but-2-yne\(^{38}\) (2b) and thus establishing the intermediacy of 4-aryloxymethylchrom-3-ene (6b) in the Claisen rearrangement of 1,4-diaryloxybut-2-ynes (2) (Scheme 22). Later intermediate allene (92) has been postulated by Schmidt et al. by the first [3,3] sigmatropic rearrangement\(^{101}\) of 1,4-diaryloxybut-2-yne.

Scheme 22

Detailed mechanistic studies\(^{102}\) have been carried out by Balasubramanian et al. A \(^1\)H-NMR follow up provided conclusive evidence for the involvement of two sequential Claisen rearrangements in the thermal
rearrangement of 1,4-diaryloxybut-2-yne (2n) to 11α-methylpterocapans (90n).

Kielman and co-workers in an attempt to synthesize 11α-methyl analogs of natural phytoalexins, such as methylhomopterocapin (90v1) to investigate their chemical and biological properties studied the thermal Claisen rearrangement of 1,4-bis(m-methoxyphenoxy)but-2-yne (2v) in detail. Substrate (2v) was subjected to refluxing in N,N-diethylaniline for several hours to give heterocyclic isomers (90v1, 90v2, 90v3 and 90v4), whose ratio is a function of reaction time and temperature (Scheme 23). The individual compounds were isolated by liquid chromatography and the composition was verified by integration of the peak areas of the methoxy and angular methyl protons (3.8 and 1.7 ppm respectively) in the 1H-NMR spectrum.

Scheme 23

Charge-induced Claisen rearrangement has been utilized by Bates and Jones for the synthesis of 11α-methylpterocarpan (90). Charge formation by co-ordination to C-C multiple bond of substrate (2) by soft Lewis acid AgBF4 in dichloromethane at 25 °C afforded selectively 4-aryloxymethylchrom-3-ene (6) or 11α-methylpterocarpan (90) depending on the substrate and the reaction time (Scheme 24).
Scheme 24

4.2.2 Synthesis of benzofuro[3,2-\(b\)]benzofurans and benzofuro[2,3-\(b\)]benzofurans.

The rearrangement of butynyl ethers (2) was sensitive to the reaction temperature, as only solvents boiling above 200 °C were found to be effective. Diethylaniline (bp 216 °C) is effective. However, addition of HCl, HClO4 or such other acids which caused a lowering of bp of the reaction medium, failed to effect the rearrangement.\(^{110}\) This problem was overcome by the addition of a solid acid e.g. 4-toluenesulfonic acid. All except four of the fourteen different ethers rearranged smoothly to give benzofurobenzofurans in good yields\(^{110}\) (Scheme 25). These results are unique in the sense that the Claisen rearrangement is carried out in a basic medium in the presence of a proton donor, leading to

\[ R' \quad \text{AgBF}_4, \quad \text{CH}_2\text{Cl}_2, \quad 25^\circ\text{C} \]

for 1, 24 h

for n, 1 h

2 l, n

AgBF\(_4\), CH\(_2\)Cl\(_2\), 25 °C

R' \quad \text{AgBF}_4, \quad \text{CH}_2\text{Cl}_2, \quad 25^\circ\text{C} \]

for 1, 1 h

for n, 24 h

6 l, n

Scheme 25

\(\text{N,N-DEA, Pts. } \Delta \)

60%

\(96\) a, H H Cl H H H Cl H

c, Cl H H H Cl H H H

d, Me H H H Me H H H

e, H H Br H H H Br H

f, OMe H H H OMe H H H

g, H H OMe H H H OMe H

h, H H phenylene H H phenylene

\(96\) a, H H Cl H H H Cl H

\(97\) a, H H Cl H H H Cl H

L, R\(_1\) = R\(_2\) = R\(_3\) = R\(_4\) = H

from an unsymmetrical 1-(4'-chlorophenoxy)-4-(4'-methylphenoxy)but-2-yn}
formation of benzofurobenzofuran system. The benzofuro[3,2-b]benzofuran (96) and benzofuro[2,3-b]benzofuran (97) may be easily distinguished from their $^1$H-NMR spectra. Compound (96d-e) shows only a single CH$_3$ signal ($\delta$ 1.7) whereas compound (97b-I) exhibits two distinct peaks (between $\delta$ 1.68 and $\delta$ 1.7 with a separation of 6 Hz) for the aliphatic methyls suggesting their non-equivalence in the structure.

Compounds (97b) and (97I) have also been described$^{111,112}$ as resulting from acid-catalyzed dehydration of 2,3-bis(o-hydroxyphenyl)-2,3-dihydroxybutanes (98). The formation of 97 from dihydroxybutanes (98) may be explained by acid catalyzed pinacol rearrangement prior to cyclization with phenolic groups (Scheme 26). It may be mentioned here that benzofuro[2,3-b]benzofuran (97) has also been synthesized by the condensation of p-cresol with glyoxal.$^{113}$

A number of benzofuro[3,2-b]benzofuran (96) and benzofuro[2,3-b]benzofurans have also been synthesized from 4-aryloxymethylchrom-3-enes (6).

Scheme 26

Scheme 27
Table: Pyrolysis of 1,4-bis(4-methylenoxy)but-2-yne (2n) in PEG-200 at 270 °C

<table>
<thead>
<tr>
<th>Reaction time (min)</th>
<th>96n (% ratio)</th>
<th>97n (% ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>46.9</td>
<td>53.1</td>
</tr>
<tr>
<td>60</td>
<td>18.2</td>
<td>81.8</td>
</tr>
<tr>
<td>90</td>
<td>9.0</td>
<td>91.0</td>
</tr>
<tr>
<td>150</td>
<td>0.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Independent pyrolysis of 6n, 90n and 96n in PEG-200 at 270 °C for 4 h yielded 97n. It was also shown that the pyrolysis of suspected intermediates, 2-(o-hydroxyphenyl)-2-methyl-3-methylenedihydrobenzofuran (101) and 3-(o-hydroxyphenyl)-4-methylenedihydrobenzopyran (102) also yielded 97n (75 %) within 2 h. Thus involvement of these intermediates in the conversion of 2 into 97 was clearly shown.

Charge formation by heteroatom complexation of substrate (90) with a hard Lewis acid\textsuperscript{114} AlCl\textsubscript{3} gave benzofuro[2,3-b]benzofuran\textsuperscript{13} (97) (thermodynamic product). No benzofuro[3,2-b]benzofuran (96) (kinetic product) was obtained (Scheme 28). Although isolation or detection of intermediates in the AlCl\textsubscript{3} catalyzed conversion of 2 into 97 was impossible it is reasonable to assume that 2 proceeds to 97 in a stepwise manner via 4-aryloxymethylchrom-3-ene (6) and benzofuro[3,2-c][1]-6a,11a-dihydro-11a-methylbenzopyran (90). These transformations may be charge-induced Claisen rearrangements similar in mechanism to the process reported for BCh.\textsuperscript{106}

Scheme 28

With aluminum chloride as catalyst 1,4-bis(m-methoxyphenoxy)but-2-yne (2v) in refluxing dichloromethane rearranged smoothly to a mixture of 96v\textsuperscript{1}, 96v\textsuperscript{2} and the corresponding cyclic ketols\textsuperscript{103} (more stable) 97v\textsuperscript{1} (major product) and 97v\textsuperscript{2} (Scheme 29).
4.2.3 Unusual ring contraction of benzofuro[3,2-c][1]benzopyran.

It has been reported that benzofuro[3,2-c][1]benzopyrans (90) undergo a novel ring contraction\textsuperscript{115,116} to give benzofuro[3,2-b]benzofurans (96) or benzofuro[2,3-b]benzofurorans (97) in 55-80 % yields under thermal condition in the presence of p-toluenesulfonic acid in boiling N,N-diethylaniline (Scheme 30).

Scheme 29

\[ \text{Scheme 30} \]

\[ \text{Scheme 31} \]
This novel ring contraction was also observed when 11a-methylpterocarpons (90) were subjected to hard Lewis acid (AlCl₃) catalysis. A plausible mechanism accounting for the transformation of 90 into 97 is outlined in Scheme 31.

Kielman et al. reported the conversion of 11a-methylpterocarpons (90¹ and 90²) into benzofuro[3,2-b]benzofurans (97¹, major product and 97²) by treatment with anhydrous AlCl₃ in CH₂Cl₂ (Scheme 32).

![Scheme 32](image)

Balasubramanian et al. have shown that the 11a-methylpterocarpons (90) undergo this novel ring contraction under photochemical condition to give 4b,9b-dihydro-4b,9b-dimethylbenzofuro[3,2-b]benzofurans (96) in 50-78 % yields (Scheme 33). This result is different from that obtained by Rall et al. from the photolysis of natural pterocarpan (106) who observed the formation of isoflavon derivatives (107) (Scheme 34). It may also be noted that the photolysis of totally different substrates viz. anthracene endoperoxides also lead to the formation of 96.

![Scheme 33](image)
Detailed mechanistic studies were carried out\textsuperscript{117} by Balasubramanian et al. on this photochemical ring contraction. An unusual acceleration of this novel photochemical rearrangement by bases has been observed. Based on literature report\textsuperscript{118,119,122-125} five different mechanisms were considered to rationalize this photochemical transformation. On the basis of exhaustive experimentation all the five mechanisms were discarded and a sixth mechanism was established for this novel photochemical rearrangement (Scheme 35). They could not offer any evidence for the butadiene intermediate (109). However, this hitherto unknown class of 2,3-bis(2-hydroxypheny)butadienes (109) can be expected to be highly photoreactive and that is perhaps the reason for their failure to detect them in the photochemical transformation of 90 to 96.

4.2.4 Synthesis of benzofurobenzoxepinone derivatives by unusual ring expansion of benzofuro[3,2-c][1]benzopyran.

11a-Methylpterocarps (90) on bromination at 6a-position with N-bromosuccinimide in carbon tetrachloride may undergo an unusual ring expansion\textsuperscript{95} to 2,8-dimethylbenzofuro[3,2-c][1]benzoxepinone (110) and its 12-bromo derivative 111 (Scheme 36). These benzofurobenzoxepinones (110 and 111) on further oxidation with N-bromosuccinimide afforded the lactone (112).
The formation of benzoxepinones (110) and (111) has been rationalized bearing in mind the cis-stereochemistry of the ring junction in 90. Benzylic bromination followed by its intramolecular displacement by the benzylic bond results in the formation of a stable cation (113). The latter (113) could lose a proton, undergo an allylic migration and give the ring expanded product (115). Oxidation of the benzylic and allylic methylene by N-bromosuccinimide affords 110 and further bromination at C-12 gives the bromo derivative (111) (Scheme 37).

4.3 Synthesis of polyheterocycles by sequential [3,3] sigmatropic rearrangements.

Synthesis of tetracyclic oxygen heterocycles has so far been discussed. Recently the synthesis of a number of polyheterocycles from unsymmetrical 1,4-bis(substituted)but-2-yne substrates (116, 117, 118 and 45) by two consecutive [3,3] sigmatropic rearrangement has been reported. The second [3,3] sigmatropic rearrangement step has been useful in substrates like 66 and 68 for the synthesis of polyheterocycles.
Synthesis of polyheterocycles from 4-methyl-7-(4-tolyloxybut-2-ynyloxy)[1]benzopyran-2-one (116).

4-Methyl-7-(4-tolyloxybut-2-ynyloxy)[1]benzopyran-2-one (116) is a unique substrate for comparing the relative ease of [3,3] sigmatropic rearrangement as it possesses two comparable aryloxypropynyl moieties devoid of isolated double bond character. Substrate (116) on refluxing in N,N-diethyladiline for 20 h afforded two products (119) (35%) and (120) (15%) which were separated by column chromatography over silica gel. The products are isomeric with the starting butyne derivative (116). On the basis of spectral data and also from mechanistic considerations, two of the four structures (119, 120, 121 and 122) were tentatively proposed for the products.

The structure of the major product was established to be 4,7a,9-trimethyl-7aH,13H[1]benzopyrano[4,3-b]furano[2,3-b][1]benzopyran-2-one (119) by its independent synthesis from the thermal rearrangement of 123 (Scheme 38). The other product was found to be linearly fused from the analysis of the aromatic region of its 400 MHz 1H-NMR spectrum including homo decoupling. NOE studies on this product clearly indicated the choice of 2,8,13a-trimethyl-6H,13aH[1]benzopyrano[6,7-b]furano[3,2-c][1]benzopyran-10-one (120). A first [3,3] sigmatropic rearrangement of 116 followed by enolization, [1,5] H shift and electrocyclic ring closure may give a chromenylmethoxycoumarin (123) which then undergoes a second [3,3] sigmatropic rearrangement at the 8-position of the coumarin followed by cyclization to give the major product (119) (angularly fused) or at the 6-position of the coumarin followed by cyclization to give the minor product (120) (linearly fused) (Scheme 38). The formation of the angularly cyclized product (119) as the major and the linearly cyclized product (120) as the minor product follows the normal pattern of the reactions of derivatives of 7-hydroxycoumarin. However, a remarkable point to note here is that the first [3,3] sigmatropic shift has taken place at the aryloxypropynyl moiety in preference to the coumarinylxypropynyl moiety.

Synthesis of polyheterocycles from 6-(4-aryloxybut-2-ynyloxy)[1]benzopyran-2-ones (117).

These substrates (117a-d) are also unique as they offer scope for comparing the relative ease of [3,3] sigmatropic rearrangements of the aryloxypropynyl moiety versus the coumarinylxypropynyl moiety.
6-Aryloxybut-2-ynyloxy[1]benzopyran-2-ones (117a-d) when heated in refluxing \(N,N\)-diethylaniline for 15 h furnished 7a-methyl-13,13a-dihydro-7aH-furo[3,2-c:5,4-f]bis[1]benzopyran-3-ones\(^{135,136}\) (124a-d) in 66-75 % yields (Scheme 39).

The structure of the product (124a-d) was deduced from elemental analysis and spectral data and confirmed by its independent synthesis from 125 (Scheme 39). The formation of products (124) from 117 may be explained by a [3,3] shift at the aryloxypropynyl part of substrates (117) followed by cyclization to provide intermediate 4-(6-coumarinylmethyl)chrom-3-enes (125) (not isolated but synthesized by another route) which may then suffer a second [3,3] sigmatropic shift at the C-5 position of the coumarin followed by enolization to give phenol (127). Transformation of phenol (127) to product (124a-d) may then occur via a spirodienone-coumaran rearrangement\(^{137,138}\) (Scheme 39). The formation of angularly cyclized product in preference to the linearly cyclized product follows the normal pattern for reactions of 6-hydroxycoumarin derivatives.\(^{139}\) The nature of the product formation is unaffected by the addition of \(p\)-toluenesulfonic acid although it improves the yields (80-85 %) and reduced the reaction time (10 h). It is also interesting to note that the first [3,3] sigmatropic shift has occurred at the aryloxypropynyl moiety in preference to the coumarin-6-oxypropynyl moiety of the substrates (117a-d).
Synthesis of polyheterocycles from 7-(4-aryloxybut-2-yloyloxy)-2-phenyl[1]benzopyran-4-ones (118).

Thermal rearrangements of another set of substrates (118a-e) providing a scope for comparing the relative ease of first [3,3] sigmatropic rearrangements of the arylxypropynyl moieties with those of flavonyloxypropynyl species were studied.\(^{142}\) 7-(4-Aryloxybut-2-yn-1-ol)-2-phenyl[1]benzopyran-4-ones (118a-c) when heated in refluxing N,N-diethylaniline for 18 h gave regioselectively 7a-methyl-2-phenyl-1,3,13a-dihydro-7aH-furo[3,2-a:5,4-h']bis[1]benzopyran-4-ones (129a-c) in excellent yields (Scheme 40). The structural assignment was made on the basis of spectral data, mechanistic considerations and also from an independent synthesis starting from 4-aryloxybut-2-yn-1-ol through a sequence of reactions e.g. (i) acetate formation, (ii) Claisen rearrangement, (iii) deacetylation (iv) conversion of OH into Cl, (v) replacement of Cl by flavone-7-oxide anion to give 130a-c.

The formation of product (129a-c) from substrates (118a-c) has been rationalized by a mechanism similar to that presented in case of formation of products (124a-d) (Scheme 39). The formation of angularly cyclized product in this case follows the normal pattern for reactions of derivatives of 7-hydroxyflavone.\(^{141,142}\)

The addition of p-toluenesulfonic acid\(^{110}\) (2 mol equivalents) to the thermolysis solution of 118a did not change product formation but the reaction time was reduced (11 h). An increase in the amount of p-toluenesulfonic acid (to 10.8 mol equivalents) furnished a new product with a furo[2,3-b]furan skeleton (131a) admixed with 129a in the ratio 65:35 (total yield 68%). If the reaction is conducted for longer period (19 h), a tendency to decomposition was observed as 7-hydroxyflavone was isolated from the
Increasing the reaction time to 28 h caused total destruction and no tractable product could be isolated. Substrates (118b) and (118c) were similarly treated with p-toluenesulfonic acid, 118b giving a mixture of 129b and 131b in the ratio 20:80 (total yield 71 %) and 118c furnishing a mixture of 129c and 131c in the ratio 15:85 (total yield 78 %). Compounds (129a-c) and (131a-c) with p-toluenesulfonic acid under the same reaction condition behaved similarly to give mixture of 129 and 131 in the same ratio as stated earlier (Scheme 40).

![Scheme 40](image)

**Scheme 40**

**Synthesis of heterocycles from the sequential [3,3] rearrangement of 1-aryloxy-4-(4'-coumarinyl)but-2-ynes (45).**

1-Aryloxy-4-coumarinyl-4-oxo-2-ynes (45a, b, d, f, l-n) when subjected to thermal rearrangement in refluxing N,N-diethylaniline gave 4-methyl-3-(2-hydroxyphenyl)pyrano[3,2-c][1]benzopyran-5(4H)-ones (132a, b, d, f, l-n). The same products (132) are obtained when 4-aryloxymethylpyrano[3,2-c][1]benzopyran-5(2H)-ones (46) were refluxed in N,N-diethylaniline for 5 h. Addition of p-toluenesulfonic acid during the thermal rearrangement of 45 or 46 showed no effect on the formation of the products. Another striking difference is that the products of the second Claisen rearrangement follow a different course and resisted cyclization to give a polyheterocycle. \(^{143}\)

The formation of 132 is evidently via 46 as 46 also provides 132 under similar treatment. The formation of 132 from 46 may be explained by a second Claisen rearrangement to give phenolic products (133). One prototropic shift may convert 133 to 134. Intermediate (134) seems to be unstable due to unfavourable structure of >C=O and -CH3 on a SP^2 carbon. Here phenyl conjugation may not be
important, the coplanarity may be lost. Intermediate (134) may undergo a second prototropic shift to give finally the stable product (132) (Scheme 41).

**Scheme 41**

**Synthesis of [6,6]pyranopyran**

Recently there has been a flurry of activity on the synthesis of pyranopyrans\(^{144-150}\). It became possible to synthesize two different series of pyranopyrans from 1,4-bis(derivatives) of 1,4-dichlorobut-2-ynes by the application of sequential [3,3] sigmatropic rearrangements. Substrates (66) and (68) on first Claisen rearrangement furnished pyranoheterocycles (67) and (69). A close examination of the products of second Claisen rearrangement of these substrates (67) and (69) reveal the possibility of an [1,6] internal conjugate addition to give a cyclized product. The results are noted below.

**Regioselective Synthesis of [6c,12b,cis]-6c,7,12b,13-tetrahydro-1H-chromeno[3=B4,4=B4:4,5]pyrano[2,3-c]chromen-1-ones (135).**

1-Aryloxymethylpyrano[2,3-c][1]benzopyran-5(3H)-ones (69a, b, d-f, j) still possess an allyl aryl ether moiety and may undergo a second Claisen rearrangement. Substrates (69a, b, d-f, j) on heating in \(N,N\)-diethylaniline indeed afforded the pentacyclic polyheterocycles, [6c,12b-cis]-6c,7,12b,13-tetrahydro-1H-chromeno[3=B4, 4=B4 : 4,5]pyrano[2,3-c]chromen-1-ones (135a, b, d-f, j) in 65-75 % yields.\(^{136,151}\) The structures of these complex molecules were established from their elemental analyses, high resolution \(^1\)H-NMR and other spectral data including 2D, DEPT, HETCOR and NOE experiments. The pyranopyran ring junction stereochemistry is found to be cis from \(^1\)H-NMR studies and also from molecular mechanics calculations. The formation of the products (135) from 69 may be rationalized by [3,3] sigmatropic
rearrangement of 69 to 136 followed by enolization to give 137. The phenol (137) in N,N-diethylaniline base may then add to the diene-lactone moiety by a [1,6] conjugate addition to give finally the [6,6] pyranopyran (135) (Scheme 42).

![Scheme 42](image)

**Scheme 42**

Regioselective synthesis of [6,6] pyranopyran from 8-aryloxymethyl-1,3-dimethyl-6H-pyrano[3,2-d]pyrimidine-2,4-diones (67).

The synthesis of 8-aryloxymethyl-1,3-dimethyl-6H-pyrano[3,2-d]pyrimidine-2,4-diones (67) has been described earlier. These substrates also possess an allyl aryl ether moiety and in principle should undergo a second Claisen rearrangement. To test this, the substrates (67a-d, f, g) were refluxed in N,N-diethylamine for 3 h and new products were obtained. The structure of the products were assigned on the basis of elemental analyses and spectral data including $^1$H, $^1$H-COSY and HETCOR. The cis-stereochemistry of the ring junction was established from decoupling, NOE experiments and molecular mechanics calculations. The cis-isomer was found to be more stable than the trans-isomer by ~3.76 kca/mol. Substrate (67g) did not provide a product arising out of cyclization but an intermediate (141g) was isolated only in 20 % yield. Substrate (67c) gave a mixture of two products (139c) (40 %) and the furopyran (140c) (40 %) (Scheme 43).

Uracil moiety is present in these heterocycles. 5-Substituted uracils have been developed as drugs.
and enzyme inhibitors but functionalization of uracil at C-5 and C-6 usually requires rather tedious and sophisticated reaction conditions. These pyranopyran derivatives have the potential to be useful. However, no biological evaluation of these compounds have been made so far. The methodology described is simple as well as facile for the synthesis of these compounds. Attempt to synthesize pyranopyran from 3H-pyran0[2,3-c]quinolin-5(6H)-ones (73) were of no avail. On heating in N,N-diethylaniline the substrates (73a, b, d-i) were converted to 1-aryloxymethyl-2-methylfuro[2,3-c]quinolin-4(5H)-ones (85a, b, d-i) in 66-79 % yields by an unusual ring contraction. However, synthesis of furo[2,3-c]quinolin-4(5H)-one derivatives has also been reported earlier in low yields.

ACKNOWLEDGEMENT

We are thankful to CSIR (New Delhi) and UGC (New Delhi) for financial assistance.

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Received, 10th July, 1998